UNITED STATES DEPARTMENT OF COMMERCE
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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/249,671	05/26/94	HAUPTMANN R	0652.1350000

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ART UNIT	PAPER NUMBER
1812	9

DATE MAILED: 09/08/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-23 are pending in the application.
   Of the above, claims 10-16 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-9, 17-23 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-23 are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☒ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☒ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

1. Receipt of the preliminary amendment filed 30 October 1994 is acknowledged. Receipt is also acknowledged of the petition, filed 26 May 1995, to accept photographic figures; a decision on this petition will be the subject of a separate communication.

2. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-9 and 17-23, drawn to methods of expressing IFN-α in *E. coli* and obtaining purified protein (classified in Class 435/subclass 69.51) and recombinant vectors for the practice of the method (435/320.1)

II. Claims 10-16, drawn to methods of purifying IFN-α (530/412).

The inventions are distinct, each from the other, for the following reasons.

Inventions I and II are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations. (M.P.E.P. § 806.05(c)). In the instant case, the combination as claimed (recombinant expression method + purification) does not require the particulars of the subcombination as claimed because a patentable distinction over the prior art can be established in the recombinant expression system *per se*. The subcombination (purification method) has separate utility for the purification of rhIFN-α from host cells other than those employed in the method of group I.

Because these inventions are distinct for the reasons given above and have acquired separate status in the art, as shown by their different classifications and because they would entail divergent searches of the research literature and consideration of unique issues of patentability, restriction for examination purposes as indicated is proper.

During a telephone conversation between Examiner S. Cermak and Applicant's attorney, Kevin Townsend, on 23 May 1995, a provisional election was made without traverse to prosecute the invention of group I, claims 1-9 and 17-23. Affirmation of this election must be made by applicant in responding to this Office action. Claims 10-16 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to non-elected inventions and/or species.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

3. The filing of an information disclosure statement on 15 November 1994 (Paper No. 7) is acknowledged. However, the form PTO-1449 and copies of the cited documents have become separated from the application file. Applicant is requested to provide a copy of the form 1449 and, if possible, copies of any cited non-patent documents. The Examiner has ready access to copies of U.S. and foreign patents; the submission of duplicates of these documents should not be necessary to permit their consideration. The Examiner apologizes for the inconvenience and thanks Applicant and Applicant's representative in advance for their assistance in reconstituting the IDS to permit the cited information to be properly considered.

4. The following technical errors in Applicant's Sequence Listing were corrected by the PTO Scientific and Technical Information Center: the hard return between "APPLICANTS:" and the name of the first inventor was deleted at field (1)(i), and the title at field (1)(viii) was edited to conform to the standard "ATTORNEY/AGENT INFORMATION". Please note the changes made so that similar errors may be avoided in future.

5. The disclosure is objected to because of the following informality. Appropriate correction is required.

The specification is confusing, *e.g.*, at pages 7-8 in that the amino acid sequences listed as SEQ ID NO: 5 and SEQ ID NO: 7 appear to be identical, whereas the context of their recitation suggests that they should represent alternative embodiments of the invention. Clarification is requested.

6. The use of trademarks, *e.g.*, Sepharose™, has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology (note the use of the trademark in claim 5). Review and amendment of the specification is requested in order to identify and appropriately delimit all trademarks.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

7. It is suggested for the sake of clarity that independent claim 17 be amended to provide the same definition for the acronym "STII" as is provided in claim 1.

8. Claims 1 is identical in scope and content to claim 23, and claim 21 is identical to claim 22. All of these claims are therefore objected to as being duplicate claims. The limitations of claims 1 and 23 delimit the same scope of embodiments, while claims 21 and 22 are *verbatim* identical. One of each set of duplicate claims should be cancelled. See 37 C.F.R. § 1.75(b); Applicant's attention is also directed to M.P.E.P. § 706.03(k).

9. Claims 1-9, 21, and 22 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and the claims dependent therefrom are confusing and indefinite as they recite that the "signal sequence of the [STII] gene" is a component of the vector employed. The signal sequence employed by the invention is a feature of the translation product, not of the vector; claim 1 should properly make reference to a sequence encoding the STII signal sequence.

Claim 4 is incomplete and indefinite in describing each of steps (c) and (d) as "performing exchange chromatography"; presumably, one of the steps is cation exchange and the other is anion exchange.

"[S]aid cation exchange chromatography" in claim 6 and "said anion exchange chromatography" in claim 7 both lack antecedent basis in claim 4.

Claims 9, 21, and 22 are vague and indefinite with respect to the term "consisting essentially of" to refer to structural features of unitary molecules, *i.e.,* DNA molecules. "Consisting essentially of" has a well-grounded meaning in patent practice to refer to the active principles of heterogeneous compositions; however, it has no established meaning relative to parts of single molecules. The Examiner suggests that in these instances, "comprising" would be an appropriate alternative.

Claims 21 and 22 are furthermore confusing and indefinite as they make reference to sequences which are more than about "70% homologous" to the reference sequence. Homology is employed in the art to describe an evolutionary relationship; in contrast to sequence identity, "homology" is meaningless when recited in a quantitative context. The same claims are furthermore confusing as they refer to "said homologous".

10. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

11. Claims 1, 2, 17, 18, and 23 are rejected under 35 U.S.C. § 103 as being unpatentable over Miyake *et al.* (*JB* 97: 1429-36, 1985) in view of Fuh *et al.* (*JBC* 265: 3111-15, 1990) and Morioka-Fujimoto *et al.* (*JBC* 266: 1728-32, 1991).

Miyake discloses a vector comprising a human IFN-α cDNA sequence ligated to a sequence encoding the *E. coli* phoA signal sequence and under the control of a phoA promoter (abstract). The vector was employed to obtain correctly processed, active rhIFN-α which was secreted into the periplasmic space of the bacterial host cell (pages 1429-30), albeit in relatively low yield (abstract). The use of an STII signal sequence is not disclosed.

Fuh discloses an expression cassette comprising the phoA promoter and a sequence encoding the STII signal peptide sequence (abstract). The heterologous protein studied, a polypeptide corresponding to the extracellular domain of the human growth hormone receptor, was properly processed and folded in the *E. coli* host (abstract), and the hGH receptor gene fragment was expressed at a much higher level than had been observed for the same gene fragment mammalian expression systems (page 3111, col. 2).

Morioka-Fujimoto is relied upon as it discloses comparisons of the efficiency of various eukaryotic signal sequences for expressing human EGF in *E. coli*. In particular, it teaches that of several native and modified signal sequences which were studied, the sequence for STII was most effective for obtaining rhEGF from *E. coli* (page 1728, col. 2; page 1730, Table II).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to construct an expression vector for IFN-α according to Miyake, replacing the phoA signal peptide-encoding sequence employed by that reference with the STII signal sequence, thus to make the expression cassette taught by Fuh, because Fuh teaches that this expression cassette affords high levels of the heterologous protein product, and further because Morioka-Fujimoto

teaches that of several signal sequences tested, the STII sequence was by far the most effective for the production of a recombinant protein. The artisan would have considered the results of the latter reference to be especially pertinent to the problem of producing rhIFN-α because that paper dealt with the production of another cytokine, rhEGF. The artisan accordingly would have expected to realize significantly enhanced protein production with the phoA promoter-STII signal peptide cassette. Given the recombinant expression of rhIFN-α, it would have been *prima facie* obvious to the artisan to purify it by conventional methods. The claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

12. Claims 8, 9, and 20-22 are rejected under 35 U.S.C. § 103 as being unpatentable over Miyake, Fuh, and Morioka-Fujimoto as applied to claims 1, 2, 17, 18, and 23 above, and further in view of Hauptmann *et al.* (US 4,917,887).

Hauptmann is relied upon as it evidences that the amino acid sequence and corresponding nucleic acid sequence of hIFN-α2 were known in the art (see the "top" sequences bridging cols. 3-5). The prior art amino acid and nucleic acid sequences are identical to SEQ ID NOs: 5 and 6, respectively.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the hIFN-α sequence of Miyake with the hIFN-α2 sequence disclosed by Hauptmann in a vector incorporating the STII signal peptide sequence, as suggested by Fuh and Morioka-Fujimoto, because Hauptmann evidences that the IFN species it encodes was known in the art to be useful. The claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

13. Claims 3 and 19 are rejected under 35 U.S.C. § 103 as being unpatentable over Miyake, Fuh, and Morioka-Fujimoto as applied to claims 1, 2, 17, 18, and 23 above, and further in view of Stephens *et al.* (US 4,769,327).

Stephens evidences that the incorporation of ribosome binding sites (RBSs) in expression vectors was well-known in the art and furthermore teaches that it is desirable to employ an RBS which is native to the host cell to be employed (col. 2, lines 5-29).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to additionally incorporate into the expression vector suggested by Miyake, Fuh, and

Morioka-Fujimoto an RBS because, as evidenced by Stephens, it was known in the art to be desirable to employ such sites in conjunction with a promoter in a bacterial expression vector. It furthermore would have been obvious to the artisan specifically to employ the *E. coli* STII RBS in conjunction with the STII signal sequence, which was known in the art at the time of the invention, because these functional components were known to function in concert in the bacterial STII gene and because Stephens teaches the desirability of employing an RBS which is native to the host cell employed. The artisan would reasonably have expected the incorporation of such an RBS to enhance the efficiency of the vector suggested by Miyake, Fuh, and Morioka-Fujimoto. The claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

14. Claims 4-7 are rejected under 35 U.S.C. § 103 as being unpatentable over Miyake, Fuh, and Morioka-Fujimoto as applied to claims 1, 2, 17, 18, and 23 above, and further in view of Protasi *et al.* (US 5,066,786) and Higashi *et al.* (US 4,828,990).

Protasi discloses a method for purifying interferons, disclosed to be applicable to IFNs generally, comprising adsorption of crude IFN onto a silecious material and elution of the product therefrom (abstract).

Higashi evidences that anion exchange, cation exchange, and phenyl[agarose] chromatography were conventional and well-characterized methods for purifying recombinantly produced proteins and teaches that proteins having IFN activity may be purified using these methods (abstract; col. 17).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to purify rhIFN-α produced according to the suggestion of Miyake, Fuh, and Morioka-Fujimoto by any methods known in the art for the purification of IFNs, including adsorption on a silecious material as suggested by Protasi or anion exchange, cation exchange, or hydrophobic interaction (phenyl) chromatography, as suggested by Higashi, because these techniques were known to be useful in the purification of recombinantly produced IFNs. It would have been *prima facie* obvious to employ any commercial available matrices known to be useful in these procedures, *e.g.*, silica gel and phenyl-, sulfopropyl-, and DEAE--Sepharose™ or Sephadex™. The artisan would have expected that these techniques, optionally in combination with any other known methods for the purification of IFN-α, would have afforded a purified, active product.

The claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

15. No claim is allowed.

16. Any inquiry concerning this communication should be directed to David Fitzgerald, who can be reached by any of the following means:

Telephone	(703) 308-3934	
Fax - Art Unit 1812	(703) 308-0294	☎ **note the new fax number**
Internet	dfitz@uspto.gov or dfitz@pioneer.uspto.gov	

Examiner Fitzgerald is generally available Mondays through Thursdays from 8 a.m. to 5 p.m. (Eastern), and during the same hours on alternate Fridays. If he is not available to take a call, a message may be left on his voicemail. Should attempts to reach him be unsuccessful, his supervisor, Garnette D. Draper, may be reached at (703) 308-4232.

Note that papers of record may be submitted to Group 1800 by fax; refer to 1096 OG 30. Submission of a confirmation copy through the mailroom is **not** required; duplicate submissions are discouraged since entry of two copies of the same paper will tend to confuse the record. Applicant should, however, retain on file the original copy of any formal paper which is submitted by fax.

The Group now maintains several fax machines. While papers may be submitted to any of these, the use of the number noted above will facilitate the matching of papers for this Art Unit with the appropriate cases. To expedite the delivery of draft or informal papers, such communications should be clearly marked on the first page as DRAFT, COURTESY COPY, or the like. It is also a good idea to call the Examiner when an urgent communication is faxed so that he knows to expect it.

The Examiner checks his e-mail messages at least every morning. Please note that Internet e-mail is NOT considered to be secure. There is at present no procedure which allows for the submission of formal communications to the PTO by e-mail.

Inquiries of a general nature should be directed to the Group 1800 receptionist at (703) 308-0196.

DAVID L. FITZGERALD
PATENT EXAMINER
GROUP 1800

5 September 1995